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REVIEW

Amyloid Cardiopathy and Aortic Stenosis

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ABSTRACT

Cardiac amyloidosis (amyloid cardiomyopathy, CA) is an increasingly diagnosed condition which is most frequently seen in older patients with heart failure and preserved ejection fraction as well as in those with biventricular hypertrophies and tight aortic stenosis (AS). Almost 15% of patients with tight AS can also have CA ATTR, an element with diagnostic, prognostic and therapeutic significance.

The CA diagnostic, associated with AS or not, is laborious and it should be made on the basis of determining the severity of the associated AS, depending on the case. The presence of both ventricular hypertrophy (≥15 mm) and red flags indicates a high suspicion of CA. Extra tests, bone scintigraphy and an absence of light free chains in blood or urine have a high specificity and sensitivity for diagnostic. Genetic investigations identify the senile or hereditary ATTR type.

Pharmacologic treatment of CA with heart failure has some peculiarities, including stopping or careful usage of beta-blockers, non-dihydropyridine calcium blockers, and angiotensin system inhibitors. Diuretic treatment, which is almost always necessary, must preserve euvolemia.

Replacing the aortic valves through transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) is recommended in tight AS associated with CA. The comparative results between the two methods of AVR favor TAVR, although perioperative complications are more frequent when the latter is used. Ongoing comparative studies of TAVR versus SAVR could define the options.

Lately, pharmacological agents targeting CA ATTR can significantly change the management of ATTR amyloidosis.

Keywords: amyloid, cardiomyopathy, aortic stenosis, markers, diagnosis, management, review.

GENERALITIES

Amyloidosis is a disease characterized by the deposit of insoluble proteins that aggregate in the extracellular space, disrupting the cellular structure and affecting the function of the plagued organs. The amyloidogenic protein deposit forms predominantly in the heart, resulting in a condition named cardiac amyloidosis (CA) or cardiomyopathic amyloid (CMA), a progressive disease with a variable clinical expression.

The interest in understanding and diagnosing amyloidosis, especially CA, increased due to observations and studies published in the last few years. Thus, a raise in amyloidosis incidence in some forms of heart failure (HF) in elders (ICE) has

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been seen. The association between CA and tight aortic stenosis (CA-AS) for approximately one in eight patients with tight AS (1), the development of image techniques that allow an accurate diagnostic of CA without morphologic exams, and the discovery of pharmaceutic agents effective against the most common type of amyloidosis (ATTR) have been signaled.

This work aims to make a relatively short presentation of current data regarding CA and the clinical implications of research and therapy of CA-AS association.

In almost 100% of cases, ATTR amyloidosis is the result of the presence of transthyretin (TTR) with cardiac tropism and CA ATTR development. The damage to other organs is unusual.

There are two genetic types of TTR: senile TTR (wild type – wtTTR) and hereditary or variable TTR (vTTR) (2). Transthyretin is a plasmatic protein synthesized by the liver; it initially exists a tetramer which, through a fragmentation process, forms fibrillar and amyloidogenic substances that deposit in the myocardial tissue and other cardiovascular structures. The wtTTR type is more prevalent in people over 80 years old, the age at which AS is most common, while the vTTR type is a genetic autosomal dominant disease which is most frequently seen in younger people. The identification of the ATTR type that leads to cardiac amyloidosis is done through genetic analysis, but the phenotype of CA that develops is similar for wtTTR and vTTR.

In light-chain (AL) amyloidosis, the amyloidogenic protein at fault is composed of light loose chains of immunoglobulin, typically produced by the plasmocyte cell clone or, rarely, in some malignancies of the B cells. Light-chain amyloidosis is a systemic disease which typically affects the heart (about 70% of cases) but it can also result in damage of the kidneys (50% of cases), liver (16%), skin, gastrointestinal tract, etc (3).

Amyloid cardiopathy has a clinical, morphologic, and hemodynamic expression that is similar in AL amyloidosis as well as ATTR amyloidosis, resulting in a restrictive cardiomyopathic phenotype.

Prevalence

There is limited prevalence data on CA, either isolated or associated with aortic stenosis. Cardiac amyloidosis is an underdiagnosed disease due to the complexity of evaluations for the confirmation of the diagnostic and its confusion with other types of cardiopathies. Amyloid detection through necropsy or myocardial biopsy examination is signaled in 25% of people over 80-85 years old and increases with age (4). Amyloid is also detected in patients with moderate or severe AS by using diagnostic tools such as biopsy during surgery or bone scintigraphy. In multiple studies, the identification of ATTR in patients with CA-AS ranged between 16% and 13.9% (5, 6).

In a more recent study from 2011, on patients with severe AS (age 83.4 +/- 6.5), CA-AS has been found in 11.8% of the diagnosed patients through bone scintigraphy and exclusion of AL CA.

Amyloidosis cardiomyopathy was identified in elderly patients with preserved EF in HF in a postmortem study on 109 patients, of whom 17% had myocardia wtTTR deposits, suggesting an amyloid etiology for the HF (8).

Amyloid cardiomyopathy appears phenotypically as a non-obstructive hypertrophic cardiomyopathy. The presence of ATTR has been detected in 5% of the 298 patients initially diagnosed with HCM *via* a scintigraphic evaluation and cardiac MRI (9).

In summary, complex specific investigation allows the identification of CA in patients with moderate to severe AS, HF with preserved EF and biventricular myocardial hypertrophy unexplained by the hemodynamic and genetic factors.

PATHOPHYSIOLOGY

The deposit of amyloid substance occurs in the myocardial tissue interstitium, valves, atrial walls, and cardiac microvasculature. Amyloid infiltration starts at the base of the heart, towards the apex, and results in a concentric biventricular hypertrophy, which in its progress leads to a hemodynamic disorder of the restrictive cardiomyopathy type. Ventricular hypertrophy is accompanied by a decrease of ventricular relaxation (diastolic dysfunction) and relatively early by damage to the systolic longitudinal function.

At an echocardiographic evaluation, CA leads to the type of HF with preserved EF and diastolic dysfunction of different degrees.

ATTR can especially infiltrate the sigmoid aortic valves, and in evolution, after calcification, it presents with moderate to severe AS. The factors that favor amyloid infiltration of the valves are

presumed to be the raise in cardiac afterload LV in AS, which would favor the deposit of fibrillar amyloid, or the raise in shear stress in AS, which could determine the deposit of amyloid. The association of the CA and AS is significant in HF with preserved EF.

Amyloid infiltration is also produced at an atrial level (including the interatrial septum), a situation accompanied by atrial tachyarrhythmia, especially atrial fibrillation (AF). The occurrence of AF reduces the filling of the ventricles even more. The mechanical remodeling of the atrium increases the thrombotic risk.

Amyloid infiltration of the heart microcirculation contributes to ischemic damage and myocardial dysfunction up to an aspect of ischemic cardiomyopathy, while the coronary epicardial arteries are unaffected (10).

In summary, the heart infiltration with ATTR can lead to the development of multiple clinical aspects: 1) HF with biventricular hypertrophy and preserved EF; 2) moderate or tight AS with AF and biatrial dilatation; and 3) restrictive cardiomyopathy with progressive to advanced HF.

Amyloid TTR cardiomyopathy, whether associated with AS or not, can be accompanied by some elements that highly suggest amyloidosis: carpian canal stenosis, spinal lombar stenosis, biceps tendon rupture and sensorial or autonomic neuropathy.

DIAGNOSIS

The CA diagnosis, associated or not with AS, is underestimated in clinical practice. The causes for the late diagnosis are linked to the relatively reduced incidence of the illness (8-12 cases *per* one million people *per* year), the non-specific nature of symptoms and the confusion with other cardiovascular diseases encountered in practice. For example, in a study, approximately 35% of people who were misdiagnosed with CA, the most frequently mistaken diseases have been hypertensive cardiomyopathy (35%), hypertrophic cardiomyopathy (23%), ischemic cardiomyopathy (11.8%), HF with preserved EF (8.8%) and aortic stenosis (8.9%) (12).

The CA diagnosis, associated with AS or not, is composed of the evaluation and diagnosis of both CA and AS.

In practice, many imagistic and biologic tests are used for either formulating a high suspicion or confirming the CA diagnosis (echocardiography, electrocardiography, nuclear magnetic resonance, bone scintigraphy and cardiac scintigraphy, or biological data). Each of these tests brings elements which together lead to the correct diagnostic.

Echocardiography

Echocardiography is the first test for a CA and AS diagnosis. Echocardiographic modifications are almost specific in advanced CA, but less specific in the early stage, when CA cannot be differentiated from other infiltrative or hypertensive cardiomyopathies (11).

The most important echocardiographic modifications in CA include (13-15): (1) growth in thickness of the ventricular walls (usually >15 mm or >12 mm), growth of the myocardial mass and reduction of ventricular size; interventricular septum >12 mm; (2) growth in myocardial echogenicity (granular aspect), which is not a specific or sensitive aspect for CA; (3) infiltration of the interatrial septum and growth of the aortic and mitral valve; (4) the echocardiographic aspect of diastolic ventricular dysfunction and increase in filling pressure with specific parameters; decrease in tissular diastolic velocity (e') and increase of the E/e' fraction (>14-15); (5) LVEF preserved until advanced stages and early damage to the LV longitudinal contraction; (6) decreased systolic longitudinal strain with a specific pattern (apical sparing), in which the apical region of the LV looks almost like a normal strain in comparison with the progressive decrease in median and base regional values (rap-2/1) (E); the apical *versus* base systolic longitudinal strain pattern differentiates CA from other pathological LVH conditions (*e.g.*, AHT, Fubry disease) and acts as an independent survival predictor; (7) hypertrophic VD with systolic dysfunction; growth in volume and diameter of AS and VD.

The two amyloidosis types, ATTR and AL, produce similar echocardiographic modifications, with differences regarding the progression of amyloid infiltration (dynamic chances in echocardiography) and the relatively fast development of HF in AL CA. The echocardiography evaluates not only the presence and severity of AS but also the eventual specific elements of ATTR. In practice, the evaluation of AS severity is done according to the current valvulopathy guidelines (USA ISC guideline).

In patients with both CA and AS, tight less than 1 square cm, low flow, low transvalvular gradient

(under 40 mm Hg) AS is found in 56% of patients, with a beat volume of <35 mL/square meters, and eventual calcification of the aortic valve with an Agathon score >2 000 (in males).

Approximatively 50% of patients with both CA and AS with low atrial flow and low gradient have preserved LVEF, paradoxically.

Are there other echocardiographis differences between tight AS and CA AS?

An analysis was performed in a study on 407 patients who had TAVI performed with an age of 83.4 +/- 6.5 years; CA AS was diagnosed in 11.8% of all subjects based on common tests plus bone scintigraphy (7).

In patients with CA AS *vs* isolated AS there have been certain particularities: more advanced age (three years); more frequently males; higher prevalence of carpal tunnel syndrome; increased NT pro BNP and HS-TNT; lowered Sokolow-Lyon voltage; ventricular remodeling with increased chamber hypertrophy; more severe diastolic dysfunction; and lower beat volume and more pronounced sparring pattern in systolic longitudinal strain;

The difference between isolated AS and CA AS needs more tests beyond echocardiography.

Electrocardiogram

Electrocardiogram (ECG) signals some diagnostic elements in CA.

Microvoltage is a classic sign present in about 35-40% of patients with CA ATTR. In the presence of LVH, the progression of microvoltage can be a sign of evolutivity in CA. Aspects of pseudomyocardial infarction, AF, atrial paralysis, AV block can also be encountered.

The development of an AV block in relatively young people and an aspect of LVH or biventricular hypertrophy suggests the possibility of CA, that has to be confirmed through further tests.

Cardiac magnetic resonance (CMRI)

It is the standard imagistic test in CA evaluation, which provides structure and functional data and myocardial tissue characteristics, complementary to the echocardiographic tests. Furthermore, it offers the possibility of differentiating CA from other cardiomyopathic causes accompanied by mural hypertrophy and has the potential for detecting early damage in CA.

Also, MRI evaluation provides other morphological and functional data: the presence and degree of ventricular hypertrophy, biatrial dilatation and beat volume, LVEF and eventually the presence of a degree of pericardial effusion. It additionally provides information on LGE and evaluates the increase in extracellular volume in CA (15).

Using the gadolinium contrast agent in CA, CMRI estimates the subendocardial and possibly transmural aspect. Both aspects are present in ATTR and CA. The transmural LGE aspect has prognostic value, with a two-ear better survival in senile ATTR *vs* hereditary ATTR (18).

Comparing the results of the endomyocardial biopsy with the common LGE has shown an 85-90% sensitivity of the imagistic method.

The CMRI evaluation has limits regarding its technical availability, the presence of both AF and renal dysfunction, and impossibility of differentiating between AL and CA ATTR (18).

Radionuclide investigation

Radionuclide investigation (RNI) using Tc 99-PYP/DPD/HMDP radiotracers has become a unique diagnostic method for CA ATTR as well as for differentiating from both AL cardiopathy and other affections accompanied by ventricular hypertrophy. Furthermore, it allows the non-invasive diagnosis of ATTR with a high accuracy, avoiding endomyocardial biopsy (13).

In current practice, bone-seeking radionuclides are often used. In the absence of CA, there is no myocardial uptake. In CA, Tc 99-PYP/DPD/HMDP is captured and, at the cardiac level, the capture level comparable with bone intensity confirms amyloid infiltration (15). In AL CA, the myocardium does not uptake this radiotracer, which identifies CA ATTR. Microcalcifications are more frequent in ATTR compared to AL (19).

For the assessment of the level of uptake at bone and cardiac intensity, various parameters are used: the heart *vs* contralateral lung uptake ratio; heart *vs* whole body ratio; heart/bone ratio. Grade 0 (no uptake) to grade 3 (cardiac uptake above rib level) is used for CA ATTR diagnostic.

In a multicenter study, myocardial uptake at grades 1-3 had 99% sensitivity and 86% specificity for detecting CA ATTR. In the absence of monoclonal proteins in the serum and urine of patients, grades 2 and 3 had a specificity and predictive value of 100% for CA ATTR.

In order to facilitate CA ATTR diagnosis, bone heart scintigraphy with specific radiotracers would be indicated in (15): unexplained ventricular hypertrophy; heart failure with preserved EF; low flow/ low gradient degenerative AS in elders; bilateral carpal tunnel history; and familial amyloidosis history.

Currently, radionuclide investigations allow for the diagnosis of CA ATTR without endomyocardial biopsy gold standard with a high confidence.

Cardiac biomarkers

Troponins and NT pro BNP are cardiac biomarkers that have been studied in CA ATTR in relation with myocardial damage and cardiac function. Later, they have been used for staging and their prognostic significance (21).

In the Mayo system for staging and prognosis, cutoff values for troponin T higher than 0.05 ng/mL and NT pro BNP >3 000 ng/L have been used as cardiac biomarkers – for stage 1, the absence of increased values; for stage 2, the presence of one of the two biomarkers; for stage 3, increased values for both biomarkers (22). The average survival in ATTR CA has been 60, 40 and 20 months for stages 1, 2 and 3, respectively (23). Another system of staging uses NT pro BNP values and eGFR. The results were similar to the Mayo system.

Cardiac biomarkers can quickly evaluate the cardiac disease and CA progression and could possibly play a role in diagnosing CA ATTR (21).

The multitude of clinical and investigative elements used together (echo, ECG, cardiac MRI) suggests, within limits, the suspicion for CA. Grouping the most significant signs and symptoms has enabled amyloidosis specialists to formulate synthetic criteria for suspecting CA. For this, red flags have been established.

Criteria for suspected CA (red flags)

A first red flag, simplified for ATTR cardiomyopathy, is shown in the "red flags for ATTR CM" table (after 24): 1) decrease of the longitudinal strain with a sparring aspect; 2) difference between LVH and QRS voltage (lack of ECG signs of LVH); 3) atrioventricular block in the presence of an increased ventricular wall thickness; 4) echo phenotype of hypertrophy associated with infiltrated aspect, including increased thickness of the atrioventricular valves, interatrial septum and free wall of the right ventricle; 5) in CMRI, a marked expansion of the extracellular space and diffuse late enhancement of gadolinium uptake, particularly subendocardial; 6) symptoms of neuropathy and/or dysautonomia; 7) increase in the troponin values at repeated evaluations.

Another easier possibility of indicating the diagnostic with a large probability (25) includes a mandatory increase in the ventricular wall of the left ventricle, without dilatation, accompanied by more than one "red flag".

In order to detect CA AS, a score that incorporates five factors has been proposed. Each factor is separately graded at between one point and three points (the RAISE score). These factors include remodeling (LVH and/or diastolic dysfunction), age, injury (hsTnT), systemic determination (carpal tunnel syndrome), and RBBB or low voltage. The RAISE score can significantly differentiate between isolated AS and CA AS. A score ≥ 2 and ≥ 3 has a high sensitivity (93,6% and 72.3%, respectively) and specificity (52.1% and 83.6%, respectively) for the presence of CA AS (7).

In order to confirm AL or ATTR amyloidosis, scintigraphic and genetic evaluation are also necessary. In the algorithm from Figure 1, the methods that lead to the diagnostic of amyloid cardiomyopathy and its type (including the genetic type) are shown.

Of equal importance to the CA evaluation algorithm is the algorithm for the diagnosis of CA in aortic stenosis, shown in Figure 2.

Endomyocardial biopsy

Endomyocardial biopsy (EB) is considered the gold standard for CA ATTR diagnostic, with 100% sensitivity and specificity if two conditions are met: (1) specimens are collected and analysed from four or more places; and (2) Congo red tests are performed for the detection of amyloid (25).

In case there are doubts and unmatched results with other CA ATTR tests, the definitive identification of misfolded proteins can be achieved through immunohistochemistry and laser dissection combined with mass spectroscopy (10).

Bioptic fragments can be obtained from other tissues identified through bone-heart scintigraphy or, for example, through abdominal fat sampling. The sensitivity of CA ATTR is double for these types of biopsy, and fat sampling has only 15% sensitivity in the case of wtTTR (26).

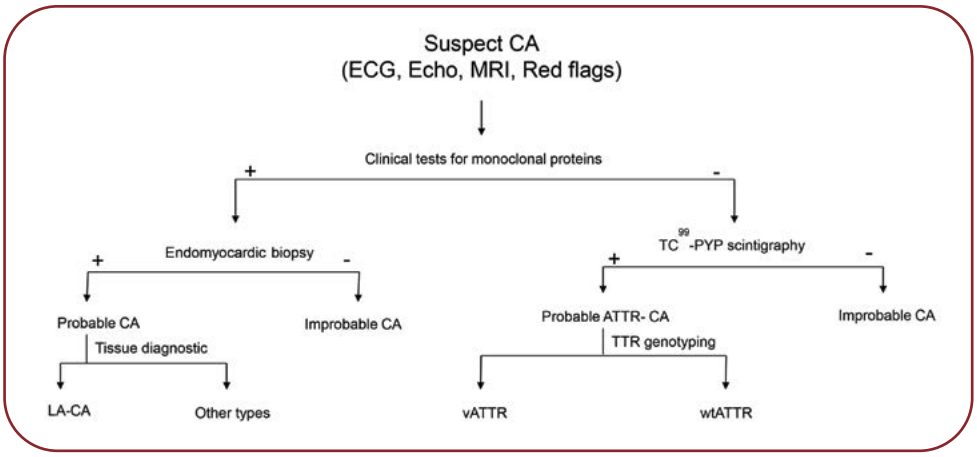

FIGURE 1. Algorithm for CA evaluation, modified after (10)

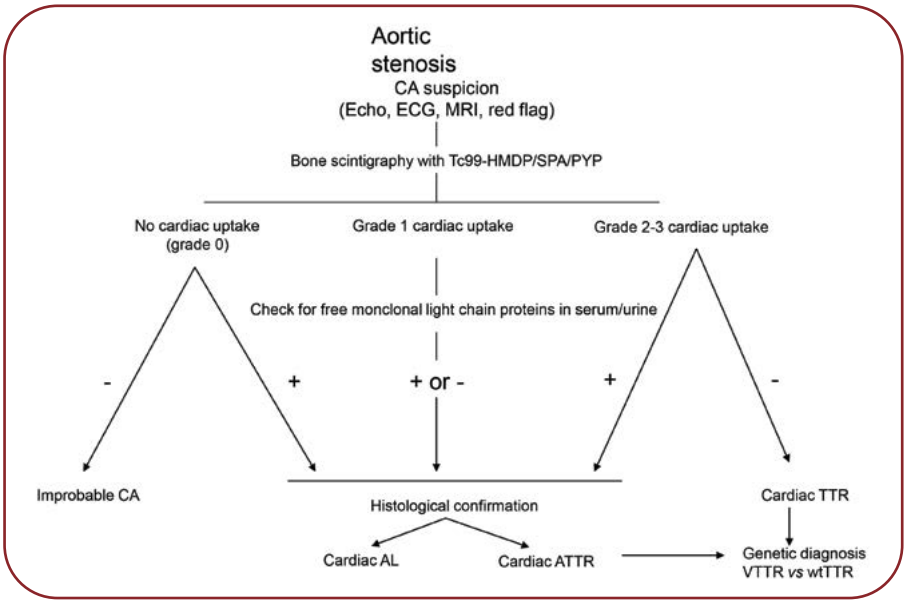

FIGURE 2. Algorithm for the diagnosis of CA in AS, modified after (1)

COMPLICATIONS

Complications can appear in the evolution of CA, especially atrial fibrillation (AF) and conduction blocks, which need to be correctly evaluated and treated.

Atrial fibrillation, a frequent arrhythmia in CA, can be novel, persistent, permanent, with high or low frequency. Treatment is not different from non-valvular AF with or without HF, as recommended by current guidelines. It is a firm anticoagulant indication (anti-vit K or DOAC) at any values of the CHA_2-DS_2-VASc score. Anticoagulants do not have an indication in the case of wide AS and sinus rhythm except for the presence of thrombi in the left atrium appendage thrombi. Prolonged anticoagulation has a high risk of bleeding through angiopathy (11).

Atrial fibrillation conversion to SR is usually done electrically. In order to maintain RS, post-conversion amiodarone is preferred, which has a high safety profile in CA ATTR (31).

For AF ablation therapy in CA there are few published studies and the issue is still being researched.

The AV or intraventricular conduction tissue infiltration can determine severe arrhythmias which need to be correctly diagnosed through Holter monitorization. Usually, a permanent and eventually prophylactic cardiac stimulator is advised, according to the ACC-AHA guidelines.

In some special situations (ventricular tachyarrhythmias) for CA management, the implantation of an ICD is necessary.

In summary, therapeutic management of CA ATTR is used to control the cardiac manifestations of the illness (heart failure, arrhythmia, thromboembolism) and to eliminate the iatrogenic effects of medication.

EVOLUTION AND PROGNOSIS

The natural history of amyloidosis cardiomyopathy is one of progressive primary cardiomyopathy leading to HF.

ATTR cardiomyopathy has a slower evolution than AL CA, which is explained by the cardiotoxicity of the free light chains in AL CA (27).

The evolution of CA ATTR depends on the age of onset, hereditary or senile ATTR phenotype, association with aortic stenosis and other comorbidities.

The onset age of the disease is earlier in AL CA than senile ATTR and the evolution to cardiac dysfunction is relatively fast (months). The average survival period in CA vATTR is shorter (2.5 years) compared to CA wtATTR (over 3.5 years) (25). The CA vATTR is often accompanied by relatively severe autonomic neuropathy which can mask the degree of cardiac damage.

The association of CA with tight AS adds negative prognosis factors, and in this case the evolution is determined by the progression of the CA.

In a study that followed the evolution of 183 patients with severe AS, CA incidence was of 25%, especially in elders (aged over 80). After a 19-month follow-up, mortality was 35%, with a higher level in CA AS than isolated tight AS (56% *vs* 20% *per* year; $p<0.0001$); the negative prognostic factor in CA AS was amyloid cardiomyopathy (28).

Another study evaluated the difference between mortality in CA AS and isolated AS in 407 patients with AS and a mean age of 83.9 +/- 6.5 years. In the majority of patients, a TAVR device was implanted (81.6% *vs* medical treatment 15.9%). Mortality after 1.7 years has been noted in 23% of patients. After one year, mortality was higher in all patients with AL CA than those with isolated AS (24.5% *vs* 13.9%, $p=0.05$).

Survival in AL CA post-TAVR was not different than isolated AS, suggesting that TAVR improved survival as opposed to medical treatment (7).

In summary, the cited research suggests that CA AS association has more severe prognosis than isolated AS and TAVR improves survival as opposed to medical treatment. The severity of CA seems to be the negative prognosis factor in the CA AS association.

ATTR HF progression often presents with intracardiac conduction disorders, especially in vATTR (approximately one in three cases), and with atrial arrhythmias in 40-60% of patients with a recent diagnostic (29).

Amyloid neuropathy can be accompanied by syncope or arterial hypotension favoured by antihypertensive treatment or beta-blockers.

MANAGEMENT OF CA ATTR

The management of CA ATTR has common elements with that of other cardiomyopathies, with heart failure and conserved EF, but also specific treatment elements. The CA AS association raises new issues for treatment decisions.

The management of CA ATTR approaches include: (1) pharmacologic treatment of the cardiac dysfunction, eventually with intracardiac devices; (2) special indications for TAVR or SAVR for CA with tight to moderate AS association; (3) organ transplant; and (4) specific medication for ATTR amyloidosis.

Pharmacologic therapy for CA HF is the most highly recommended in the USA ISC guidelines for heart failure. The four types of drugs (ACEI or ARB, beta-blockers, diuretics and MRA or ARNI) are only conditionally usable in HF with preserved EF and diastolic dysfunction and especially in CA-tight AS association (especially in low flow/low gradient AS).

a) Diuretic therapy is the first line medication in case of symptomatic, decompensated HF (furosemide, torsemide, bumetanide) (11). An excessive diuresis reduces the filling pressure, beat debit and cardiac debit, with negative effects on tissular perfusion, especially in the kidney. Maintaining euvolemy in heart failure conditions with a restrictive profile is an important objective in CA heart failure.

b) RAAS inhibitors (ACEI and ARB) can be administrated conditionally, if the BP level is acceptable. Current or higher doses lead to hypotension and cardiac-renal syndrome. Autonomic dysfunction can accentuate the arterial hypotension and produce orthostatic hypotension.

c) Mineralocorticoid receptor antagonists can be given in association with a diuretic in conditions of acceptable BP and in the absence of renal dysfunction.

d) Beta-blockers are not to be administered as they reduce the cardiac frequency – an essential element in maintaining the cardiac debit during restrictive dysfunction; furthermore, they have a negative inotropic action (10).

e) Other drugs used in HF treatment, including digoxin and non-dihydropyridine calcium blockers, must be stopped in heart failure because both agents irreversibly fixate to amyloid fibers and produce severe side effects (29, 30).

Therapeutic attitude in CA ATTR patients

The therapeutic attitude in patients with CA and tight AS has three possible directions: interventional, replacement of the valves (TAVR), surgical (SAVR) or medical treatment.

Currently, there are few studies published about TAVR or SAVR: a total of 516 patients with a prevalence of AS in CA between 13.9% and 16% (1). The studies are small, the main technique being TAVR and the results are usually divergent.

The majority of studies have signaled the higher risk of mortality and non-improvement of the functional status of the heart after aortic valve replacement.

A more recent study of Scully *et al* reported results from 2 000 patients hospitalised for TAVR. Tight AS with CA had a prevalence of 13.9%. In total, 101 (75%) patients had undergone TAVR and 25% received medical treatment. Periprocedural complications were similar for isolated AS and CA AS groups. Mortality after 19 months was similar in the two groups (21% *vs* 27%, p=0.71). Functional evolution was favorable for the whole cohort (p<0.01) but also for the CA AS (p=0.03). The study concludes that TAVR in CA patients "is not to be avoided" (5).

Other studies have signaled that TAVR in patients with CA ATTR would have a higher risk of procedural complications due to the fragility of tissues infiltrated with amyloid (32); regardless of the valvular replacement method in tight AS associated with CA, there are negative prognostic risk factors: EF<50%, severe reduction of the longitudinal strain (>=10%), severe diastolic dysfunction (grade 3) and low flow, low gradient AS (33).

Currently, a preference for TAVR in patients with tight AS associated with CA is emerging in high or intermediate surgical risk conditions. Two ongoing studies will signal the TAVR *vs* SAVR results. Furthermore, the expansion of the use of target therapy in CA ATTR (Tafamidis & Patisiran) will bring results that will modify therapeutic management in patients with CA AS (1).

Organ transplant (liver, heart) is very rarely recommended in CA when the current therapeutic methods do not yield a result.

Specific medication for CA ATTR

Decoding the role of amyloidogenic proteins in ATTR has stimulated research of the discovery of some pharmacologic agents that act specifically through either stabilizing TTR tetramers or decreasing hepatic production of TTR. TTR tetramers become amyloidogenic when they are dissociated or selectively cleaved into monomers. Stabilizing the tetramers and stopping the fragmentation process could lead to a decrease in the formation of fibrillar amyloidogenic aggregates.

Tafamidis is one such molecule which sticks selectively to the binding site of TTR thyroxine, decreasing the dissociation of TTR tetramers into monomers and its aggregation into fibrillar amyloidogenic proteins. The efficiency and safety of administering Tafamidis has been proven in ATTRACT, a multicenter study on patients with CA ATTR. Treatment with Tafamidis has led to a reduction in all-cause mortality by 13% *vs* placebo. It has decreased cardiovascular hospitalisations and improved the six-minute walking test. Favorable effects have been obtained in patients with HF grades I and II NYHA but in grade III (34). Thus, the study suggests the importance of an early CA ATTR diagnostic for the optimization of results.

Tafamidis is approved by FDA for ATTR cardiopathy treatment.

Currently, more therapeutic agents with different action mechanisms are being studied.

Diflunisal is a non-steroidal anti-inflammatory drug with a stabilizing effect on TTR and partial results in amyloidosic polyneuropathy. Its side effects – water retention, possibly nephrotoxicity – but also the limited results do not recommend it.

Two new agents, Patisiran and Inotersen, act by decreasing hepatic TTR production (10, 1). Patisiran acts by interfering with ARN. Inotersen is an antisense olygonucleotide inhibitor. Both agents significantly reduce hepatic TTR production by 81% and 29%, respectively, and are used with favorable effects for amyloidosis neuropathy. Patisiran has been used in the APOLLO study for amyloidosis neuropathy. Sub-analysis has shown a reversal of cardiac remodeling, improvement of cardiac output, decrease of the NTproBNP level, but without decreasing mortality or cardiovascular hospitalisation (35).

Current research with new molecular therapeutic targets could bring new elements of efficiency in ATTR cardiomyopathy, including AS in amyloidosis. ❑

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References

1. **Ternacle J, Krapf L, Mohty D, et al.** Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. *J Am Coll Cardiol* 2019;74:2638-2651.
2. **Maurer MS, Hanna M, Grogan M, et al.** Genotype and Phenotype of Transthyretin Cardiac Amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol* 2016;68:161-172.
3. **Saith SE, Maurer MS, Patel AR.** Systemic Amyloidosis due to Monoclonal Immunoglobulins. *Cardiac Involvement Hematol Oncol Clin North Am* 2020;34:1055-1068.
4. **Tanskanen M, Peuralinna T, Polvikoski T, et al.** Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. *Ann Med* 2008;40:232-239.
5. **Scully PR, Patel KP, Treibel TA, et al.** Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J* 2020;41:2759-2767.
6. **Scully PR, Treibel TA, Fontana M, et al.** Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement. *J Am Coll Cardiol* 2018;71:463-464.
7. **Nitsche C, Scully PR, Patel KP, et al.** Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. *J Am Coll Cardiol* 2021;77:128-139.
8. **Mohammed SF, Mirzoyev SA, Edwards WD, et al.** Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2014;2:113-122.
9. **Damy T, Costes B, Hagège AA, et al.** Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients with increased left ventricular wall thickness. *Eur Heart J* 2016;37:1826-34.
10. **Yamamoto H, Yokochi T.** Transthyretin cardiac amyloidosis: an update on diagnosis and treatment. *ESC Heart Fail* 2019;6:1128-1139.
11. **Kittleson MM, Maurer MS, Ambardekar AV, et al.** Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. *Circulation* 2020;142:e7-e22.
12. **González-López E, Gagliardi C, Dominguez F, et al.** Clinical characteristics of wild-type transthyretin cardiac amyloidosis: disproving myths. *Eur Heart J* 2017;38:1895-1904.
13. **Dorbala S, Cuddy S, Falk RH.** How to Image Cardiac Amyloidosis: A Practical Approach. *JACC Cardiovasc Imaging* 2020;13:1368-1383.
14. **Falk RH, Plehn JF, Deering T, et al.** Sensitivity and specificity of the echocardiographic features of cardiac amyloidosis. *Am J Cardiol* 1987;59:418-422.
15. **Dorbala S, Ando Y, Bokhari S, et al.** ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 2 of 2-Diagnostic Criteria and Appropriate Utilization. *J Card Fail* 2019;25:854-865.
16. **Galat A, Guellich A, Bodez D, et al.** Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? *Eur Heart J* 2016;37:3525-3531.
17. **Sperry BW, Vranian MN, Hachamovitch R, et al.** Are classic predictors of voltage valid in cardiac amyloidosis? A contemporary analysis of electrocardiographic findings. *Int J Cardiol* 2016;214:477-481.
18. **Fontana M, Pica S, Reant P, et al.** Prognostic Value of Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Cardiac Amyloidosis. *Circulation* 2015;132:1570-9.
19. **Stats MA, Stone JR.** Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. *Cardiovasc Pathol* 2016;25:413-417.
20. **Gillmore JD, Maurer MS, Falk RH, et al.** Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. *Circulation* 2016;133:2404-2412.
21. **Pregenzer-Wenzler A, Abraham J, Barrell K, et al.** Utility of Biomarkers in Cardiac Amyloidosis. *JACC Heart Fail* 2020;8:701-711.
22. **Dispenzieri A, Gertz MA, Kyle RA, et al.** Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. *J Clin Oncol* 2004;22:3751-3757.
23. **Grogan M, Scott CG, Kyle RA, et al.** Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. *J Am Coll Cardiol* 2016;68:1014-1020.
24. **Witteles RM, Bokhari S, Damy T, et al.** Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. *JACC Heart Fail* 2019;7:709-716.
25. **Ruberg FL, Grogan M, Hanna M, et al.** Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;73:2872-2891.
26. **Quarta CC, Gonzalez-Lopez E, Gilbertson JA, et al.** Diagnostic sensitivity of abdominal fat aspiration in cardiac amyloidosis. *Eur Heart J* 2017;38:1905-1908.
27. **Falk RH, Alexander KM, Liao R, Dorbala S.** AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. *J Am Coll Cardiol* 2016;68:1323-1341.
28. **Cavalcante JL, Rijal S, Abdelkarim I, et al.** Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. *J Cardiovasc Magn Reson* 2017;19:98.
29. **Pollak A, Falk RH.** Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 1993;104:618-620.
30. **Rubinow A, Skinner M, Cohen AS.** Digoxin sensitivity in amyloid cardiomyopathy. *Circulation* 1981;63:1285-1288.
31. **Mints YY, Doros G, Berk JL, et al.** Features of atrial fibrillation in wild-type transthyretin cardiac amyloidosis: a systematic review and clinical experience. *ESC Heart Fail* 2018;5:772-779.
32. **Sperry BW, Jones BM, Vranian MN, et al.** Recognizing Transthyretin Cardiac Amyloidosis in Patients With Aortic Stenosis: Impact on Prognosis. *JACC Cardiovasc Imaging* 2016;9:904-906.
33. **Treibel TA, Fontana M, Gilbertson JA, et al.** Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. *Circ Cardiovasc Imaging* 2016;9:e005066.
34. **Maurer MS, Schwartz JH, Gundapaneni B, et al.** Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018;379:1007-1016.
35. **Solomon SD, Adams D, Kristen A, et al.** Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis. *Circulation* 2019;139:431-443.